Unclassified

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Contractor: Roger T. Sherman, M.D.
Associate Professor of Surgery
University of Tennessee

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ANNUAL REPORT AND FINAL SUMMARY REPORT

Covering the Period

31 March 1965 - 31 May 1966

Title: TREATMENT OF VESICANT AND THERMAL BURNS

Prepared By

Roger T. Sherman, M.D.

31 May 1966

Unclassified

I. Introduction

A. The following report covers work done during the period of 1 January 1965 through 30 April 1966. The previous Annual Report was submitted on 28 March 1965, so that this report is prepared 12 months after the last annual report submitted.

The report covers four areas of work during the period covered.

1. Sulfamylon skin penetration
2. Evaporational water loss studies
3. Bacteriologic studies
4. Clinical trial of Sulfamylon spray

B. Final Report at termination of contract 31 May 1966 is also attached.

II. Current Progress

A. Sulfamylon Penetration Studies

1. Rationale:

"When Lindsey first suggested the use of mafenide in studies of topical therapy of experimental open wounds, Mendelson was of the opinion that it might be particularly valuable because past studies by others implied that mafenide is poorly absorbed. It was her impression that it might remain active at the site longer, and not be as conducive to systemic toxicity as a more readily absorbed topical antibacterial agent. However, as analytical techniques have improved in recent years, it seemed worth while to re-evaluate the extent to which topically applied mafenide is absorbed systemically."

2. Procedure:

a. Gauze pads (area: 103 cm^2) or absorbent beaker pads (area: 95 cm^2) are saturated with Sulfamylon solution.

b. The quantity and per cent concentration of Sulfamylon in saline (not water) present on the pads is recorded.

c. The pads are placed on the skin of dogs which has been cleaned and shaved. The pads remain in place throughout the experiment.

d. If the dressings are to be occluded, a piece of Saran Wrap (0.0005 inch thick) or Mylar 25 (0.0005 inch thick) is taped tightly to the skin.

e. Blood or urine samples are collected from the dog at regular intervals.

f. Control blood or urine blanks are taken before any pads have been placed on the dog.

g. When urine samples are collected, an I.V. drip of D5W (10 cc/kg/hr) is used to assure good urine volume.

h. Sulfamylon was measured in blood or in urine by the method of McChesney, et al (see Annual Report 31 December 1963 — 1 January 1965, page 8).

3. Results:

a. Series I

Sulfamylon Skin Penetration

Exp. #	Dog #	Amount Sulfamylon Applied to Skin	Area (cm^2)	Samples	Time	Mg. Sulfamylon Per 100 cc Sample
1	Unburned #225	2 g - 10% soln in saline	103	Whole blood (Heparinized)	Every 30 min. for 3 hrs.	Less than 1 mg.
2	Unburned #225	2 g - 10% soln in (100%) DMSO	103	Whole blood (Heparin)	Every 30 min. for 3 hrs.	Less than 1 mg.
3	Unburned #386	2 g - 10% soln in saline	103	Whole blood (Heparin)	Every 30 min. for 3 hrs.	Less than 1 mg.
4	Unburned #457	2.5 g - 10% soln in (100%) DMSO	95	Whole blood serum plasma	2 hrs. " "	Less than 1 mg. " "
5	Burned #254	2.5 g - 10% soln in (100%) DMSO	95	Whole blood (Heparin)	1 hr. 2 hrs.	Less than 1 mg. "
6	Unburned #221	2 g - 10% soln in (100%) DMSO	95	Whole blood terminal urine	Every 15 min for 1.25 hrs.	Less than 1 mg.
7	Unburned #386	2.5 g - 10% soln in (100%) DMSO	95	Urine	30 min. 60 min. 90 min.	Less than 1 mg. 2 mg. 2 mg.
8	Unburned #457	2.5 g - 10% solr in (100%) DMSO	95	Urine	30 min. 60 min. 90 min. 110 min.	Less than 1 mg. " 3 mg. 2.5 mg.

Sulfamylon Skin Penetration Series I Continued . . .

						Blood	Urine
9	Unburned #253	30 g - 20% soln in (100%) DMSO	570	Whole blood urine	2 hrs.	Less 1 mg.	Less 1 mg.
					4 hrs.	1.6 mg.	1 mg.
					6 hrs.	1.9 mg.	3.2 mg.
10	Unburned #386	25 g - 20% soln in saline	475	Whole blood urine	2 hrs.	2.2 mg.	55.5 mg.
					4 hrs.	4.5 mg.	87.5 mg
					6 hrs.	10.4 mg.	51.5 mg.
11	Burned #432	5 g - 10% soln in saline	190 - continue adding Sulfamylon to pads	Whole blood urine	2 hrs.	Less than 1 mg.	
					3 hrs.	"	
					4 hrs.	"	
						Blood	Urine
12	Burned #391	15 g - 20% soln in saline	285 - continue adding Sulfamylon to pads	Whole blood urine	2 hrs.	Less than 1 mg.	
					3.5 hrs.	"	
					4.5 hrs.	< 1 mg.	1 mg.
13	Burned #253	20 g - 20% soln in (90%) DMSO	380	Whole blood urine	2 hrs.	< 1 mg.	6.5 mg.
					3.5 hrs.	"	22.2 mg.
					4.5 hrs.	"	28.5 mg.

b. Series II

Sulfamylon Skin Penetration						
Exp. #	Dog #	Amount Sulfamylon Applied to Skin	Area (cm^2)	Samples	Time	Mg. Sulfamylon Per 100 cc Sample
1	Unburned #7	2.8 g - 20% soln aqueous	206 Saran occluded	Whole blood (Heparin)	1.5 hrs. 2.5 hrs. 3.5 hrs.	Less than 1 mg. " "
2	Unburned #6	7.2 g - 20% soln aqueous	190 Saran occluded	Whole blood (Heparin)	Every 2 hrs. for 6 hrs.	Less than 1 mg.
3	Unburned #7	2.8 g - 20% soln aqueous	206	Whole blood	Every hr. for 3.5 hrs.	Less than 1 mg.
4	Unburned #6	7.2 g - 20% soln aqueous	190	Whole blood	Every 2 hrs. for 6 hrs.	Less than 1 mg.
5	Unburned #7	10.8 g - 20% soln - aqueous	190 Saran occluded	Whole blood	Every hr. for 6 hrs.	Less than 1 mg.

c. Series III

Sulfamylon Skin Penetration
Unburned Dogs

Dog # - Wt.	Area Covered By Dressing	Quantity Sulfamylon On Dressing	Time	Dressing Cover		
				Saran	Mylar	Open
				mg/100 cc Urine		
1 14 kg.	190 cm^2 (2 absorbent beaker pads)	9.5 grams	1 hr.	24.5	30.1	0.0
			2	61.8	50.9	0.0
			3	47.7	38.5	3.8
			4	53.4	49.0	4.5
			5	46.0	45.3	4.3
			6	33.2	42.6	2.8
2 13.5 kg. 14 kg.	206 cm^2 (2 gauze pads)	2.8 grams	1.5 hrs.	18.0	22.0	0.0
			2	26.6	25.5	0.0
			3	24.9	23.0	1.2
			4	27.7	26 7	2.0
			5	43.2	29.2	2.2
			6	22.5	28.0	1.0
3 9.5 kg	206 cm^2 (2 gauze pads)	2.8 grams	0.5 hr.	53.8	20.0	0 0
			1 hr.	99.5	97.5	0.0
			2	109.0	(99.0	2.3
			3	82.0	(	3.5
			4	84.0	87.0	4.9
			5	92.0	81.0	5.0
			6	102.0	86.8	3.7
4 14.2 kg.	206 cm^2 (2 gauze pads)	2.8 grams	1 hr.	15.2	13.0	0.0
			2	29.1	27.2	0.0
			3	22.0	26.1	1.0
			4	24.7	23.0	1.5
			5	32.6	24.7	2.4
			6	20.3	25.9	0.9

4. Discussion.

a. Series I

The first six experiments in Series I were attempts to recover Sulfamylon in blood. The data shows that both the addition of DMSO (100% and increase in the surface area exposed to Sulfamylon failed to produce measurable blood levels. Experiment #5 shows a similar result in the burned dog.

Failure to demonstrate Sulfamylon breakdown products in the blood prompted us to look more closely at urine samples. Experiments #7 and #8, basically similar to the others, reveal that at least measurable amounts of Sulfamylon breakdown products can be demonstrated in the urine when the Sulfamylon applied is added to DMSO.

The small amount of Sulfamylon breakdown products recovered in the urine prompted experiment #9 in which 20% solution in 100% DMSO applied to an area six times as large as experiment #8 to determine if the small recovery was due to the amount applied. The results are indicated in the table.

Experiment #10, similar to #9 but without DMSO, demonstrates a far larger recovery in both blood and urine and suggests that 100% DMSO may interfere with Sulfamylon absorption.

Experiments #11, #12, and #13 were done in burned dogs. Animals were burned as previously reported (see Annual Progress Report, 31 December 1962 - 1 January 1964). In experiment #12, Sulfamylon solution was continuously added to the beaker pads to obviate the problem of loss by evaporation. Despite increasing the amount of Sulfamylon applied in experiment #12 to three times that of experiment #11, very low urine recovery rates were obtained. These results should be contrasted to the unburned dog in experiment #10.

Experiment #13 reveals that unlike the control (experiment #9) addition of 90% DMSO to Sulfamylon in the burned dog permits a fair recovery in the urine.

b. Series II

All five experiments in this series demonstrate failure of recovery of Sulfamylon breakdown products under the conditions stated in whole blood. Our experience with blood samples up to and including this series prompted us to use urine samples only for the remaining experiments.

The addition of Saran Wrap covering the Sulfamylon is an attempt to stop evaporation of water from the dressing, although in burned dogs (experiments #11 and #12, Series I) continued application did not permit high urine recovery.

c. Series III

Results of the four experiments in Series III demonstrate that covering of the Sulfamylon dressing either with an impervious plastic membrane or with Mylar 25 increases the amount of Sulfamylon breakdown products which can be recovered in the urine.

d. Sulfamylon dressings with various plastic coverings are being studied in burned dogs for comparison with Series III at the time of this report.

e. Pending results from d. above, clinical trial of Sulfamylon spray and dressings covered with plastic films might well be valuable

B. Sulfamylon and Nafcillin Diffusion Chamber Studies

1. Procedure:

a. Two cup diffusion chambers were made of Teflon and so designed that one cup was separated from the other by the membrane to be tested. The chambers each have a small opening into which a Luer lock fitting is fixed. Solutions to be tested are beside each other separated by the membrane to be tested. The area of the membrane exposed was 4.9 cm^2 in four of the cells and 4.2 cm^2 in one of them (slight difference in construction). Some runs were made with the cells closed to the atmosphere. Later runs were made with the cells open (through the Luer lock) to the atmosphere as most diffusion cells used by others are.

b. Various combinations of solutions were tested in the cell under conditions of both closed and open to the atmosphere.

c. Temperature was controlled by immersion of the diffusion cells in a water bath at 37.5° C.

d. Various concentrations of DMSO were evaluated.

e. Rat or dog skin was used as the diffusion membrane. The skin was removed full thickness from the anesthetized living animal. Subcutaneous fat was excised under direct vision by a scalpel. All skin was used immediately after removal from the animal.

f. Concentrations diffused were measured at a given time in hours following the start of the test.

2. Results:

a. Nafcillin diffusion rates utilizing 0.1% concentration of Sodium Nafcillin through full thickness dog skin into distilled water with the cell closed to the atmosphere.

Aqueous Nafcillin 0.1%

Time (Hours)	Diffusion Rate (ugms/cm^2/hr)	Test Number
2	3.1	12
18	2.4	1
18.75	0.9	10
45.5	2.5	2
72	0.7	3

b. Nafcillin diffusion rates utilizing 0.1% Nafcillin in 90% DMSO through full thickness dog skin into distilled water with the cell closed to the atmosphere

90% DMSO — Nafcillin

Time (Hours)	Diffusion Rate (ugms/cm^2/hr)	Test Number
1	0	7
4	1.2	9
18	0.8	4
19	3.2	5
63.6	0.8	11

c. Aqueous Sulfamylon diffusion rates utilizing 0.1% concentration of Sulfamylon in water through full thickness dog skin into distilled water with the cell open to the atmosphere.

Aqueous Sulfamylon 0.1%

Time (Hours)	Diffusion Rate (ugms/cm^2/hr)	Test Number
19	3.7	22
19	2.55	23
19	2.6	24
19	2.7	25

d. Aqueous Sulfamylon diffusion rates through full thickness dog skin utilizing 1% concentration with the cell open to the atmosphere.

Aqueous Sulfamylon 1%

Time (Hours)	Diffusion Rate (ugms/cm^2/hr)	Test Number
23	11.5	26
23	10.8	28
23	18.0	29

e. Aqueous Sulfamylon diffusion rate utilizing 0.1% concentration in 90% DMSO through full thickness skin into distilled water with the cell open to the atmosphere. Unburned and third degree burned rat skin.

Aqueous Sulfamylon in 90% DMSO

Time (Hours)	Diffusion Rate (ugms/cm^2/hr)		Test Number
	Unburned	Burned	
20	2.2	3.6	20 & 21

3. Discussion:

a. Results in a. and b. above indicate, in essence, that the rate of diffusion, whether Nafcillin is in DMSO solution or not, is quite slow.

b. Results in c. and d. above indicate that increasing the concentration of aqueous Sulfamylon from 0.1% to 1.0% is commensurate with an increase in diffusion rate. Also, at comparable times, diffusion rates are roughly comparable with the exception of the first 19 hour run and the last 23 hour run.

c. The results in e. above cannot really be interpreted other than to note that under the conditions of the two runs the rate is slow with both burned and unburned skin (see c. above — diffusion rates at 19 hours).

d. Further studies along these lines were not carried out for three reasons. First,

the data is not so meaningful as in vivo studies. Second, the whole DMSO concept was modified by removal of this drug from the market for human use by the FDA. If toxic side effects occur, certainly large burn surfaces would provide inordinate exposure. Third, many variables inherent in diffusion chamber work are difficult to control.

C. Evaporational Water Loss Studies

1. Introduction:

Considerable data on evaporational water loss has been submitted in previous reports. See Annual Report 31 December 1962 — 1 January 1964, Annual Report 31 December 1963 — 1 January 1965, Letter Report, April 1965, etc. Various clay mineral dressings have been studied in an attempt to demonstrate their usefulness in reducing the rate of evaporational water loss from the surface of the burn wound. From the outset of this work, the clay dressings have been constructed as described in detail in the Annual Progress Report of 31 December 1962 — 1 January 1964.

The covering plastic film (Mylar 25) was selected for its porosity to serve as a membrane to reduce the rate of evaporative water loss from the surface of the wet clay.

2. Comparison Menlo Park clay with Petroria clay:

a. Procedure

Water in cylinders of known diameter (4.9 cm^2) were covered with clay dressings as described. The water does not touch the clay. Control cylinders were measured concurrently

b. Results

Control: Open beakers = 74.1 ugms/min/cm^2

Menlo Park Clay

Sample #	Rate of Loss ugms/min/cm^2
1	6.0
2	9.0
3	9.2
4	8.4
5	9.0
6	9.2
7	8.8
8	7.8

Average 8.4

Petroria Clay

Sample #	Rate of Loss ugms/min/cm^2
1	8.8
2	9.6
3	9.1
4	7.2
5	9.5
Average	8.8

c. Discussion

The remarkably similar results, despite the markedly different compositions of the clay (Menlo Park — Attapulgite, Pretoria Kaolinite) suggest, possibly, that clay composition is not a significant factor in evaporative water loss reduction.

Another possibility is that Mylar alone is responsible for the similarity of results. Experiments to test this were done.

3. Mylar film studies:

a. Procedure

Cylindres of water of known diameter (4.9 cm^2) were covered with dressings as follows. The dressings are not in contact with the water.

Wet clay (Menlo Park) with Mylar cover
Wet clay (Menlo Park) without Mylar
Mylar film alone
Complete dressing without clay

Control cylinders were run concurrently with the dressings tested.

b. Results

Control 74.1 ugms/min/cm^2

Wet Clay with Mylar Film

Sample #	Rate of Loss ugms/min/cm^2
1	6.0
2	9.0
3	9.2
4	8.4
5	9.0
6	9.2
7	8.8
8	7.8

Average 8.4

Wet Clay without Mylar

Sample #	Rate of Loss ugms/min/cm^2
1	20.1
2	21.4
3	20.7
4	20.1

Average 20.6

Mylar Film Alone*

Sample #	Rate of Loss ugms/min/cm^2
1	3.8
2	3.9
3	3.5
4	3.8
5	3.7

Average 3.8

*Film placed on the cylinder and then held in place by rubber band.

Complete Dressing without Clay**

Sample #	Rate of Loss ugms/min/cm^2
1	18.7
2	24.9
3	27.2
4	29.0
5	23.8

Average 24.7

**See Annual Progress Report 31 December 1962 — 1 January 1964, Appendix F-1

c. Discussion

From the above results, it is clear that the covering which reduces the rate of evaporational water loss the best is Mylar 25 alone. The figures for the complete clay dressing and for the complete dressing without the clay are comparable.

It should be noted that these experiments are subject to some variation due to changes in room temperature and humidity during the runs. Controls, however, were subject to the same varying conditions.

This work would seem to make the "clay concept" less desirable as a method for reducing the rate of evaporational water loss than anticipated. Further data on the efficacy of Mylar 25 alone or in modified forms has been demonstrated by Dr. Jelenko.

The "clay concept" may still have some real value in the control of surface infection in burns.

D. Bacteriologic Studies

Preliminary bacteriologic studies were done by Mr. F. B. Brinkley at Edgewood Arsenal.

1. Tests on autoclaved samples as indicated in the table. In vitro tests are also presented.

2. Results

Test	Attagel	X1585	Wyoming
1. Pure culture of B. Subtilis* diffused through 0.3 cm of sterile sample on agar plate	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs.
2. Pure culture of B. Subtilis mixed with sterile sample and placed on agar plate	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs.

*The pure culture of B. Subtilis was taken from an agar plate on which it grows well.

In Vitro Results of Clay Samples

Test	Kamp's Clay	Wyoming Bentonite	Attagel*	X1585
Pure culture of Staph. aureus (209) diffused through 0.3 cm of sterile samples on mannitol salt agar	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs	Growth plus fermentation of mannitol within 24 hrs.	No growth at 24 or 48 hrs.
Pure culture of E. coli (B_6, D_{26}) diffused through 0.3 cm of sterile samples on MacConkey's agar	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs.
Pure culture of B. strept. (C_{203}) diffused through 0.3 cm of sterile samples on blood agar	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs.	No growth at 24 or 48 hrs.

*The Attagel appeared to absorb the broth cultures very well but the other samples would not.

E. Clinical Study of Sulfamylon Spray

1. Procedure:

a. Consecutive patients with thermal burns admitted to the John Gaston Hospital

were selected for study.

b. Treatment with 10% solution of sterile Sulfamylon HCl in distilled water was applied twice a day by spraying and was instituted as soon as possible after admission. Approximately 30 cc of solution/M^2 was used at each treatment.

c. Surface cultures were taken at intervals during therapy and blood studies were done as indicated.

d. Close clinical observation was carried out in all patients.

2. The Series:

Thirty-one patients were studied. Twenty-two were children, the youngest being one year old. The remainder of the series were adults with the oldest being 112 years. Eleven were males and 20 were females. The majority of patients were Negro.

3. Etiology:

Twenty-four burns were produced by flame (77.7%) and seven by hot liquids (22.3%).

4. Burns 0-10%

Name	0-10%	Age	Total Hospital Days	Days to Graft	No.
Sherman	8	9	69	26	1
Vernadine	10	3	28	18	2
Marion	5	7	34	19	3
Avery	5	9	39	19	4
Roderick	10	3	13	None	5

5. Burns 11-20%

Name	11-20%	Age	Total Hospital Days	Days to Graft	No.
Kay	20	3	16	18	1
Robert H.	15	55	67	33	2
Pearline	15	8	58	32	3
Janice	15	1	16	None	4
Gwendolyn	20	5	66	22	5
Demetria	15	3	42	25	6
Darlene	20	6	39	25	7
Mary E	20	6	38	29	8
Will	15	74	55	36	9
Sarah	20	112	21D*		10
Willie Mae	12	39	28	20	11
Willie L.	15	46	37	23	12

6. Burns 21-30%

Name	21-30%	Age	Total Hospital Days	Days to Graft	No.
Willie W.	30	8	30	None	1
A. B.	25	62	71	35	2
John	25	11/2	70	35	3
Annie	30	6	Still in	24	4
Joyce	25	7	"	46	5

7. Burns 31-40%

Name	31-40%	Age	Total Hospital Days	Days to Graft	No.
Darius	35	2	86	33	1
Pansy	40	6	58D	39	2
Veither	40	60	36D	29	3
Nellie	35	45	28D		4
Abe	40	4	25D		5

*Death

8. Burns 41-50%

None

9. Burns 51-60%

Name	51-60%	Age	Total Hospital Days	Days to Graft	No.
Vicki	60	7	11D		1
Delsie	60	74	6D		2
Paul	60	2	19D		3

10. Burns 61-70%

None

11. Burns 71-80%

None

12. Burns 81-90%

Name	81-90%	Age	Total Hospital Days	Days to Graft	No.
Otis	90	4	4D		1

13. The Deaths:

a. 20% - 40%

Name	Age	% Burn	Day of Death	Cause of Death
Sarah	112	20	21	Accidental
Nellie	45	35	28	Sepsis
Pansy	6	40	58	Sepsis
Veither	60	40	36	Myocardial infarct
Abe	4	40	25	Sepsis

b. Discussion

There are 15 burns in the 20% - 40% group. There were ten survivors and five deaths, a mortality of 33.0%. This figure cannot be compared to the 30% mortality reported for burns of comparable size by Moncrief, et al (Arch. Surg., 92:558, 1966) unless deaths in our group not related to sepsis or not adequately treated with Sulfamylon are excluded.

When these cases are excluded there remain ten patients with burns of 20% - 40% with one death.* The series is still too small to compare with the results from the S.R.U. at Fort San Houston.

The following are the case reports of patients whose deaths may be considered as not related to sepsis or why had inadequate Sulfamylon therapy.

SARAH: A 112 year old female suffered 20% second and third degree flame burns. She was started on Sulfamylon spray b.i.d. on the day of burn and treated for five days with I.V. fluids. She did well during the 21 days she was in the hospital. Surface cultures of her burn wound at intervals revealed a number of organisms (Staphylococcus aureus, Proteus mirabilis and rettgeri, E. coli, etc.), but no Pseudomonas was ever cultured. Her daily temperature (mean) for the week prior to death was 98^{6}. Two days before death she developed a slight rash on her back, but therapy was not stopped. Her serum chlorides never exceeded 109 mEq/L. Her eschar on daily tub baths was separating well and at no time was any gross evidence of infection. The eschar was dry at all times. Despite her advanced age, we fully expected this patient to recover from her burn when on the 21st day after burn she was left unattended in the bath tub and apparently drowned. Autopsy — cause of death, drowning. No sepsis.

NELLIE: A 45 year old female mongoloid who suffered 35% third degree flame burns. She was started on Sulfamylon spray (b.i.d.) the day of her burn. She was treated with I.V. fluids for four days. For the first 12 days after burning, she did well with a clean, hard, dry eschar grossly uninfected. Surface cultures at intervals up to this time had revealed organisms (Staphylococcus aureus, Proteus vulgaris, E. coli, and also the yeast Candida albicans), but no Pseudomonas. On the 12th day after burning, she developed a severe rash over her entire body which was accompanied by an increase in fever to 101° and some disorientation. I.V. fluids were reinstituted and her medication stopped. (Sulfamylon was the only drug being used.) Within two days her surface cultures became positive for Pseudomonas and three days after cessation of Sulfamylon spray, gross infection was evident. The rash was improved at that time and Sulfamylon was resumed. The rash by the next day was worse than originally, almost resembling an exfoiliative dermatitis.

*Nellie

Cultures of the surface revealed a number of organisms, including Pseudomonas. We were forced by her severe skin reaction to stop Sulfamylon again. She rapidly developed evidence of severe burn wound sepsis and died on the 28th day after burning despite systemic antibiotics, I.V. fluids, etc. It is not known whether this patient had received prior sulfonamide drugs.

This case can be called "inadequate Sulfamylon therapy," as gross infection was not apparent until the Sulfamylon was discontinued. However, the inadequate treatment was because of Sulfamylon sensitivity and, therefore, this case probably should be included in the total mortality figures.

PANSY: A 6 year old girl admitted with 40% second and third degree body burns sustained when her clothing caught on fire. She was in prior good health. Sulfamylon spray was started and continued for the first 27 days after burning. During this period, the eschar remained grossly clean and was debrided serially. The patient maintained a mean daily temperature of 103° F. - 104° F. daily despite absence of gross infection. Her white blood cell count remained in the range of 16,000 per cu.mm. Surface cultures taken at intervals showed a variety of organisms, including Pseudomonas, on all but the first culture. She developed a severe upper respiratory infection during the first week of admission. By the 28th day after burning, all of the eschar was off and althought she continued to run her high fever, she showed no clinical evidence of burn wound sepsis.

She was dressed at this time and Sulfamylon discontinued. Skin grafting was delayed on a number of occasions by her high fever thought (on clinical grounds) to be due largely to pneumonia. A portion of her burn was autografted 10 days after Sulfamylon was stopped. A surface culture 20 days after Sulfamylon was stopped showed Proteus rettgeri and Streptococcus fecalis. She developed edematous rales, continued her high febrile course, and on the 58th post burn day had severe G.I. bleeding (Hct. 19 mm) with death on that day, 40 days after Sulfamylon was discontinued and the surface ready for grafting.

VEITHER: This 60 year old woman sustained a 40% second and third degree body burn when her clothing ignited. She had had a cerebral vascular accident some time prior to her burn. She lived 36 days after her burn and received b.i.d. Sulfamylon spray on each day from admission to death. Surface cultures revealed a variety of organisms, including an otherwise unidentified clostridial organism on the 10th post burn day. Pseudomonas was cultured for the first time on the 16th post burn day and remained present in surface cultures thereafter. The eschar remained clean and dry during the stage of debridement, but on the 28th post burn day there was some gross infection in the few shreds of eschar remaining. Her mean daily temperature remained essentially below 100° F. until the 29th post burn day when she spiked to 104° F. Granulation tissue appeared grossly clean at that time, but surface cultures that day revealed

five organisms. On the 30th post burn day she developed much difficulty with lung secretions, and on the 35th a tracheostomy was done. An EKG was interpreted as myocardial infarct shortly before the patient died on day 36. Her granulation tissue was not clinically grossly infected at that time.

ABE: A 4 year old boy with flame burn of 40% third degree of his body. This patient is categorically excluded as he was treated with Sulfamylon spray, but only late (14 days post burn) when he was included in our patient load. His burns were infected He died nine days later with blood cultures positive for Streptococcus fecalis and Aerobacter.

It would be quite fair to remove all of the above patients from the series on the grounds that either their death was not due to sepsis, or that Sulfamylon was not ideally applied.

14. The Living:

a. Ten patients with burns of 20% - 40% of the body surface survived. One of the benefits of Sulfamylon spray therapy was demonstrated in this group. The following case is typical of others in the series.

WILLIE W. The 8 year old boy suffered deep (thought to be third degree) partial thickness burns of 30% of the body surface when boiling water was spilled on his clothes. Sulfamylon spray and I.V. fluids started on day of burn. Surface cultures on the third post burn day showed no growth. By the 10th post burn day, his white blood cell count had risen from 16.6 to 32.6. however, his burn was grossly quite clean. Pseudomonas and Staphylococcus aureus were cultured that day. Mean daily temperature at approximately 101° F. over the first 10 days. This wound would have ordinarily converted to full thickness burn from infection, but this did not occur. Epithelial islands were seen on the 13th post burn day and complete spontaneous coverage was achieved on 30th post burn day.

15. Burns 41% - 90%

a. Four patients are in this group. One (Otis) of 90% surface burn is uniformely unsalvageable. The other three had burns of 60% of the body surface and all were flame burns.

Name	Age	% Burn	Day of Death	Cause of Death
Delsie	74	60	6	Renal shutdown
Vickie	7	60	11	Renal shutdown Sepsis
Paul	2	60	19	Sepsis - Melena
Otis	4	90	4	No sepsis

b. Discussion

Both Vickie and Delsie had renal shutdown. Vickie had very deep (4th degree) thermal burns, and her wounds appeared grossly infected on the 8th post burn day with surface cultures showing five organisms, including Pseudomonas. Mean daily temperatures were 102° F. - 103° F., and her chlorides slowly rose (108 - 136 mEq/L). No urinary output from day 3.

It is impossible to tell what part sepsis played in this patient, nevertheless, gross evidence of infection was present.

Delsie did not show any gross evidence of infection on day 6 when she expired. Surface cultures that day showed Aerobacter and Strep fecalis. She also was in renal shutdown, and her chlorides rose from 110 mEq/L to 140 mEq/L.

16. Hospital Stay:

a. Duration of hospitalization for removal of the eschar is reported to be lengthened by the use of Sulfamylon. It is not unusual to see densely adherent, grossly uninfected eschar still present 8 to 10 weeks after injury (Moncrief, et al, Arch. Surg., 92:558, 1966). The comparison figures on hospital stay at the John Gaston Hospital were taken from a study of 242 burns of 20% or more of the body surface admitted between 1955 and 1960 to our hospital and reported by Jackson and Lee (Arch. Surg., 87:937, 1963). The comparison is below.

Duration Hospitalization (Survivors)

Weeks	JGH 1955-1960		Spray	
	% of Pt.	No. of Pt.	% of Pt.	No. of Pt.
0-2	10	15	4.5	1
2-4	11	16	13.3	3
4-8	40	58	36.3	8
8-12	20	30	31.8	7
12-16	8	12	4.5	1
16-20	3	5	0	
20-24	4	6	0	
6 mos.+	2	3	0	

b. Discussion

The series at this point is still too small to make a valid comparison.

17. Conclusions:

a. Twice daily Sulfamylon spray is distinctly advantageous in the initial period of burn therapy for second and third degree burns. It prevents significant infection and prevents conversion of deep second to third. At this time our series contains insufficient numbers of burns from 40 to 50% to show valid statistics supporting this point. Unfortunately, in our series, five patients with burns of about 40% died, however, it is not felt that this was due in any case to failure of Sulfamylon spray.

b. The eschar formed under this therapy is hard, dry, and difficult to remove.

This could be advantageous under less than optimum conditions, as in disaster situations, as the protective covering remains in place until it is desired to remove it.

c. Application of the spray (10% Sulfamylon in distilled water) is painful for most patients with second degree burns, but the pain does not last long (approximately ten minutes).

d. There was no hyperchloremia in any patient except those with renal shutdown.

e. Skin reactions, one of which was very severe, occurred in three patients. None occurred before the 12th day of therapy.

f. Reports of cultures bear no obvious relationship to the clinical appearance of the burn, except that dry eschars usually show Staphylococcus. Pseudomonas appeared in surface cultures at some point or other in the progress of nearly all patients. There were, however, no deaths from Pseudomonas sepsis. We cannot compare our results with the results of others at this time as our series is too small, particularly in burns of from 20% to 50%. No distinct relationship between temperature elevation and cleanliness of the eschar was demonstrated.

g. Second degree burns (superficial dermal burns) epithealize more rapidly with Sulfamylon spray than with any other method we have ever used.

h. Yeast infections of the eschar occurs under Sulfamylon therapy, but is of probably no clinical significance.

i. B.i.d. Sulfamylon spray will be used as policy for the next 12 months on all burn admissions.

III. Final Summary Report

A. Introduction

Work under contract DA-18-108-CML-7113 was begun in June 1962 at the termination of a one year grant for development of an expedient treatment for vesicant burns. During the period of effort, the original objectives of this research contract have gradually changed in emphasis because of the results of study of experimental vesicant burns. The original objective was seemingly of major importance as a high degree of incapacity from relatively small areas of vesicant burns, e.g., scrotum, axilla, or hands, in combat troops would seem empirically to be a problem. Because flame burns and their treatment are also important to the military, efforts for the evaluation of various forms of therapy for these injuries were carried out.

B. Vesicant Burns

Vesicant burns were made on the forearm of a number of volunteers. At various intervals after burning, fluid was aspirated from the blisters and analyzed for total protein, sodium, potassium, chloride, and calcium. Comparison was made between serum levels and blister fluid levels. (Data in Semi-annual Report, 1 February 1963.) The benign nature of vesicant burns in volunteers in every instance determined a reappraisal of the incapacity which might be produced under combat conditions. There was remarkable absence of infection and prompt, uncomplicated healing in every instance. This raised the further question that any treatment which might be applied to these experimental burns could not improve on the observed clinical course. It is most important to avoid a poorly conceived generalization that a proposed treatment of experimental vesicant burns would, a priori, be beneficial to similar burns sustained in combat. An exhaustive search was made for description of actual combat ineffectives resulting from vesicant burns. Review of medical literature (including classified material), as well as correspondence with medical officers on active duty in WW I was unproductive of any verified experiences with vesicant burns. No documented experience was discovered concerning incapacity, clinical types, degree, or treatment of vesicant burns obtained in actual combat. Report no. 42 CD (Aust.) 20 May 1944, Assessment of Casualties from Vesicant Agents (classified) was the only comprehensive study of the effects of vesicant agents under combat conditions discovered. A motion picture illustrating this report (unclassified) was carefully appraised. It was concluded that the problem of possible combat ineffectives following vesicant exposure would seem relatively unimportant. In any case, the symptoms and healing pattern of small experimental blisters utilized in our experiments could in no way be compared to combat vesicant burns. Reports of simulated H burns indicate that incapacity, i.e., hospitalization, was required for skin burns, especially genital, but in nearly every case the exposure (ct) necessary to produce skin lesions of such magnitude was also sufficient to produce symptoms of systemic toxicity. The proposed condition of intensive study of vesicant blister fluid was altered because of this to include work with thermal burns. Histologic study of excised vesicant burns was not done, as a comprehensive study of serially excised H burns at intervals up to 38 days had already been done (see OSRD 3620 and OSRD 3620-A).

No apparent difference in healing of II burns in a human volunteer was seen when DMSO was used to treat the burn and a control without treatment was compared.

C. Thermal Burns

Two primary routes of investigation were pursued. The first, study of evaporative water loss and its possible effect on the hypermetabolic syndrome of major burns, and, second, various forms of topical therapy for thermal burns. An apparatus for the direct measurement of evaporational water loss was developed. Many experiments were carried out with the apparatus (data in Annual Report, 1 February 1964). Reproducibility, however, was not satisfactory. Improvements of this apparatus by Dr. Cark Jelenko has established it as a very accurate method for the measurement of evaporational water loss.

An apparatus using standard laboratory heat gun for producing thermal burns in volunteers was described (see Annual Progress Report, 1 February 1964). One further apparatus was also developed in an attempt to deposit antibiotics beneath the eschar of third degree burns. This apparatus utilized nitrogen under high pressure to force antibiotic solutions through tiny holes in the nozzle into the sub-eschar layers. A prototype of such an apparatus was described (see Appendix E, Annual Progress Report, 1 February 1964). It is the impression of the Investigator that such an apparatus could be perfected, however, the success of topically applied Sulfamylon would make the time and effort to do so not very rewarding. Data obtained reveal evaporational water loss through third degree burn surfaces to be about 20 times control. Methods for reducing evaporational water loss were tested with primary emphasis on the use of Fuller's earth. Clay dressings reduce the rate of evaporational water loss and in vitro adsorb bacteria readily. To date, Mylar 25, by itself, has been the most efficient membrane for reduction of evaporative water loss.

D. Sulfamylon Studies

Penetration of the skin, both burned and unburned with various concentrations of Sulfamylon, with and without DMSO, was studied. Some work with diffusion chambers was done, but reproducibility with the technique is not very good. Data on skin penetration by Sulfamylon is tabulated in the Annual Report, 31 March 1962 - 31 May 1966. A clinical study of 10% Sulfamylon spray was started and the results of the first group of patients is encouraging, however, as yet, a large enough group of patients has not been treated to draw definite conclusions.